UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,390	10/25/2005	Virginie Louvain	263989US0PCT	2517

22850 7590 01/14/2010

OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, L.L.P.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
TSAY, MARSHA M	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
01/14/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/518,390	LOUVAIN ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,9,10 and 18-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,9,10 and 18-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This Office action is in response to Applicants' remarks received November 10, 2009.

Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

Claims 1-2, 4-8, 11-17, 23-38 are canceled. Claims 3, 9-10, 18-22 are currently under examination.

Priority: The request for priority to FRANCE 0208299, filed July 3, 2002, is acknowledged. A certified copy of the foreign priority document has been filed in this case on December 30, 2004 and is in a non-English language.

Objections and Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 9-10, 18-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 3, 9-10, 18-22 are rejected under 35 U.S.C. 112, first paragraph, for a lack of structure.

The court of Appeals for the Federal Circuit has recently held that such a general definition does not meet the requirements of 35 U.S.C. 112, first paragraph. "A written description of an invention involving chemical genus, like a description of a chemical species, requires a precise definition, such as be structure, formula {or} chemical name, of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.,* 1997 U.S. App. LEXIS 18221, at *23, quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). The court held that "in claims involving chemical materials, generic formulae usually indicate with specificity what generic claims encompass. One skilled in the art can distinguish such a formula fro others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish it from others. One skilled in the art therefore cannot, as one can do with a fully described genus visualize the identity of the members of the genus".

Here, Applicants are reciting claims drawn to Factor X/Xa analogues having only the structural limitation of a 6-mer (i.e. SEQ ID NO: 9). There is no other structural limitation recited besides SEQ ID NO: 9. Additional information regarding the structure of the instant Factor X/Xa analogues or at least the source of the Factor X/Xa, i.e. human Factor X/Xa, bovine Factor X/Xa, etc., is requested.

In their remarks, Applicants assert that the presently claimed invention is drawn to a factor X presenting a very specific mutation in its activation site. The scope and nature of the

term "factor X" is well known in the art and, as such, the meaning of "factor X analogue" as described and claimed in the present application would be readily apparent to the skilled artisan in view of the disclosure of the present application. Applicant's arguments have been fully considered but they are not persuasive.

As currently written, the "factor X analogue" can encompass any protein that comprises the 6-mer peptide (i.e. instant SEQ ID NO: 9). The claims do not specify from what source the factor X is from and/or any other structural information regarding the factor X therefore, it is unclear if upon cleavage, the factor X analogue would have the same functional activity as native factor X even if it has the thrombin-cleavable sequence of instant SEQ ID NO: 9.

The instant specification has support for human factor X; therefore, if the scope of claim 3 is narrowed down to native factor X from a human source then the rejection under 112, first paragraph, written description would be overcome.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3, 18, 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Himmelspach et al. (US 6573071; previously cited).

For examination purposes, claim 3 has been interpreted as a Factor X analogue comprising the sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9). Therefore, any reference

disclosing a Factor X analogue comprising at least instant SEQ ID NO: 9 is believed to be relevant art.

Himmelspach et al. disclose a Factor X analogue, having a modified processing site, comprising the sequence Gly228 to Ile235 having the sequence Gly228-R6-R5-R4-R3-R2-Arg234-R1 (col. 83, see also SEQ ID NO: 27), wherein

a) R1 is an amino acid selected from the group consisting of Ile, Val, Ser, Thr, and **Ala**,

b) R2 is an amino acid selected from the group consisting of **Pro**, Gly, Lys, and Arg,

c) R3 is an amino acid selected from the group consisting of Phe, Lys, Met, Gln, Glu, Ser, **Val**, Arg, and Pro

Therefore, Himmelspach et al. disclose a Factor X analogue comprising the sequence Gly228-R6-R5-R4-**Val232-Pro233-Arg234-Ala235-Val236-Gly237**, wherein the amino acids in bold correspond to the instant thrombin-cleavable sequence Val-Pro-Arg-Ala-Val-Gly. Himmelspach et al. also disclose a preparation comprising said Factor X analogue having a processing site as noted by the sequence noted above, therefore said preparation would be a medicinal product (col. 84 lines 60-67). Himmelspach et al. do not explicitly teach a Factor X analogue comprising Val-Pro-Arg-Ala-Val-Gly (instant SEQ ID NO: 9).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a Factor X analogue, having a modified processing site, comprising Gly228-R6-R5-R4-**Val232-Pro233-Arg234-Ala235-Val236-Gly237**, wherein the amino acids in bold correspond to the instant sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9) (claims 3, 22). The motivation to do so is given by Himmelspach et al., which disclose Factor X analogues can

comprise a modified processing site having an amino acid sequence formula that encompasses instant SEQ ID NO: 9.

While Himmelspach et al. do not specifically teach a Factor Xa analogue, this analogue is within the scope of Factor X analogues disclosed by Himmelspach et al. since upon cleavage of the Factor X analogue of Himmelspach et al. as noted in the paragraph above, one of ordinary skill would obtain a Factor Xa analogue since the Factor X analogue of Himmelspach et al. can comprise instant SEQ ID NO: 9 (claim 18). It should also be noted that the phrase "can be obtained by cleavage of a Factor X analogue by thrombin" is also describing a property of the factor X analogue which would be present as long as SEQ ID NO: 9 is encompassed within the Factor X analogue.

The reasons for maintaining the Himmelspach et al. reference are the same as previously noted and for the reasons noted below.

In their remarks received November 10, 2009, Applicants assert the object of the present application is a factor X, initially with a native activation site, in which said activation site is mutated between the position 232 and 237.

The native sequence of the activation site of factor X comprises the sequence:

Gly_{228}-Asn_{229}-Asn_{230}-Asn_{231}-Leu_{232}-Thr_{233}-Arg_{234}-Ile_{235}-Val_{236}-Gly_{237}

The factor X according to the present invention is mutated so that the sequence Leu_{232}-Thr_{233}-Arg_{234}-Ile_{235}-Val_{236}-Gly_{237} of the native activation site of factor X is replaced with the sequence Val_{232}-Pro_{233}-Arg_{234}-Ala_{235}-Val_{236}-Gly_{237}.

The factor X analogue of the present invention thus comprises, in its activation site, the sequence:

Gly_{228}-Asn_{229}-Asn_{230}-Asn_{231}-**Val_{232}-Pro_{233}-Arg_{234}-Ala_{235}-Val_{236}-Gly_{237}**

The Examiner alleges that Himmelspach et al. disclose a factor X analogue having comprising the sequence:

Gly_{228}-**$R6_{229}$**-$R5_{230}$-$R4_{231}$-Val_{232}-Pro_{233}-Arg_{234}-Ala_{235}-Val_{236}-Gly_{237}

According to Himmelspach et al., R4 can be Asn, R5 can be Asn, but Himmelspach et al. do not disclose the presence of Asn at position 229 (amino acid R6).

Applicant's arguments filed have been fully considered but they are not persuasive.

Reply: It should be noted that the thrombin-cleavable sequence is the sequence Pro-Arg-Ala (specification p. 6 lines 14-17). Therefore, even if Himmelspach et al. do not teach Asn at position 229 (amino acid R6), the thrombin-cleavable sequence Pro-Arg-Ala is still present and would be cleaved by thrombin. It should be noted again, that Himmelspach et al. disclose that their factor X analogue is cleavable by factor IIa (i.e. thrombin), which is the serine protease recited in instant claim 18. Therefore, regardless of what the other amino acids are outside of the 6-mer sequence, Leu_{232}-Thr_{233}-Arg_{234}-Ile_{235}-Val_{236}-Gly_{237} (instant SEQ ID NO: 1), since Himmelspach et al. disclose that the sequence can be replaced by Val_{232}-Pro_{233}-Arg_{234}-Ala_{235}-Val_{236}-Gly_{237} (instant SEQ ID NO: 2), it would be reasonable for one of ordinary skill to know that the instant invention is within the scope of the Himmelspach et al. invention.

Claims 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Himmelspach et al. (US 6573071; previously cited). The teachings of Himmelspach et al. are

outlined above. Himmelspach et al. further disclose nucleic acid molecules, expression vectors, and host cells that can be used to express the Factor X analogues disclosed by Himmelspach et al. (col. 17-28). Himmelspach et al. do not explicitly teach a nucleic acid molecule encoding the thrombin-cleavable sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a Factor X analogue having the thrombin-cleavable sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9) as disclosed by Himmelspach et al. by constructing expression plasmids for the preparation of Factor X analogue for expression in host cells (claims 19-21). The motivation to do so is given by Himmelspach et al., which disclose that Factor X analogues having the thrombin-cleavable sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9) can be prepared by constructing expression plasmids followed by transformation into a host cell for expressing a Factor X analogue protein.

The Himmelspach et al. reference is still maintained over claims 19-21 because it is believed to be relevant art for the reasons as noted above.

Claims 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Himmelspach et al. (US 6573071; previously cited). The teachings of Himmelspach et al. are outlined above. Himmelspach et al. further disclose Factor X/Xa is an important component of the prothrombinase complex and may be used to treat patient suffering from blood coagulation disorders, i.e. hemophilia (col. 3-4). Himmelspach et al. do not explicitly teach a preparation

comprising a Factor X analogue with the thrombin-cleavable sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9) and a method of treating hemophilia utilizing said Factor X analogue.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the Factor X analogue of Hammelspach et al. to a patient for the treatment of hemophilia because Hammelspach et al. disclose Factor X/Xa which exhibits high stability and can be activated to Factor Xa without use of conventional proteases (col. 4 lines 30-35), i.e. modified to have the thrombin-cleavable sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9), can be administered to treat patients suffering from hemophilia (claims 9-10).

The Himmelspach et al. reference is still maintained over claims 9-10 because it is believed to be relevant art for the reasons as noted above.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maryam Monshipouri/
Primary Examiner, Art Unit 1656

January 6, 2010

M. Tsay
Art Unit 1656